REMARKS

Claims 29-34 are currently pending in the application. In order to advance prosecution, Applicants have amended claims 29, 31, and 33 to more particularly point out and distinctly and clearly claim their invention. A complete listing of all the claims, in compliance with the revised amended format, is shown above. The amendments are made without prejudice, do not constitute amendments to overcome any prior art rejection, and do not present any new matter.

Discussion of the 35 U.S.C. § 103 Rejections

Claims 29, 31 and 33 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,770,195 ("Hudziak") in view of Esteva, F.J. *et al.*, Pathology Oncology Research, 7(3): 171-177, 2001 ("Esteva"), in view of Pinkas-Kramarski, Oncogene, 16: 1249-1258, 1998 ("Pinkas-Kramarski"), and further in view of Hoffmann, Cancer Immunol. Immunother., 47(3): 167-175, 1998 ("Hoffmann") (abstract only). The Applicants respectfully traverse the rejection.

An analysis for obviousness requires a determination of the scope and content of the prior art, the differences between the prior art and the claims at issue must be ascertained, and the level of ordinary skill in the pertinent art must be resolved. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). Applicants provided an analysis of the scope and content of the prior art cited by the Office Action in the Response to Office Action Mailed April 11, 2008 filed October 13, 2008. The Office apparently agrees with Applicants that none of the references themselves cited in support of the previous rejection, *that is* Hudziak or Esteva, affirmatively teach or suggest the instantly claimed methods treating a subject with cancer comprising cells that express EGFR. The Office Action additional cites Pinkas-Kramarski and Hoffmann in support of this ground for rejection. The Office Action apparently takes the position that the teachings of these references

in combination with the previously cited references motivate the skilled worker to achieve the claimed invention, *and* provide the worker with a reasonable expectation of success. Applicants respectfully disagree for the reasons set forth herein.

For the Examiner's convenience, Applicants reiterate the salient features of the claimed invention here. This invention is directed in part to methods for treating a subject with cancer comprising cells that express EGFR. These methods include, in part, the step of assaying a cell or tissue sample from the subject to detect an expression level for HER3 in cells from the cancer. Moreover, these methods, in part, require treating the subject with an anti-EGFR antibody when the detected HER3 expression level has an optical density less than 9 when the assay is quantitative immunohistochemistry. It is important to note that EGFR is otherwise known as HER1, and is a different and distinct protein from HER3.

None of the cited references, either alone or in combination, teach or suggest the instantly claimed methods. The Office Action again cites to Hudziak as disclosing a method of treating cancer that express EGFR with an anti-EGFR antibody. However, as previously noted, Hudziak does not disclose the existence of HER3, much less its use as a biomarker. In its response, the Office Action did not disagree with this observation. Also, the Office Action continues to cite to Esteva as disclosing measurement of the levels of EGFR, HER2, HER3, HER4, hergulin, p38, and pHER2. However, again as previously noted, Esteva does not teach or suggest that any of these patterns of expression can be used to select a subject with cancer for treatment with a molecule targeting EGFR. The Office Action points out that Esteva teaches that tumors that express HER-3 and HER-4 exhibit cellular growth and drug resistance. However, the only therapeutic to which these two biomarkers were said to confer resistance was doxorubicin, a therapy that does not target any member of the erbB/HER family. In fact, Esteva points out that

it is patients whose tumors overexpress HER-2 that have been shown to benefit from doxorubicin-based therapy, not tumors whose cells express EGFR. The Office Action fails to explain why a therapy whose success is predicted by HER-2 expression (doxorubicin) would correlate with a therapy whose success has been predicted by EGFR expression (an anti-EGFR antibody), much less even acknowledge that a correlation even exists. However, without such a correlation, the disclosure in Esteva regarding HER-3 and HER-4 conferring drug-resistance is irrelevant to the present invention.

Nevertheless, the Office Action continues to cite these two references in the current obviousness rejection. However, the Office Action apparently concedes that these two references alone or in combination with each other do not teach or suggest the instantly claimed invention, because the Office Action additional cited Pinkas-Kramarski and Hoffmann for this new ground of rejection. However, the deficiencies of Hudziak and Esteva are not overcome by either Pinkas-Kramarski or Hoffmann, either alone or in combination.

Pinkas-Kramarski is cited as teaching that the ErbB-2/ ErbB-3 (Her2/Her-3) heterodimer forms a binding site for ligands such as EGF and betacellulin. The Office Action alleges that this helps demonstrates that EGFR ligands stimulate growth of cancer cells via HER-3, and that it is reasonable to expect that inhibition of only EGFR in tumors with both EGFR and HER3 might be a less effective therapy than if the anti-EGFR therapy was provided to a tumor with only EGFR signaling to provide a growth signal to the tumor. In response, Applicants first note that Pinkas-Kramarski does not teach treatment with any therapy, much less a therapy based on anti-EGFR antibody as required by the present claims. In addition, the results described by the Office Action were obtained with immortalized cell lines that have unique and distinct biological properties. In order to ensure the continued survival of immortalized cells, which allow them to

grow and divide indefinitely *in vitro*, the growth properties of the cells must be altered. In addition, these immortalized cells can also be altered to either over-express or not express one ore more different proteins. For example, in Pinkas-Kramarski, one cell line that was used had the property of overexpressing ErbB-2 (HER2), while another cell line was negative for EGFR. One of skill in the art would recognize that results with such immortalized cell lines may not extrapolate to primary cells of tissue samples from a subject, as required by the present claims. In fact, the two cell lines used in a majority of the experiments in Pinkas-Kramarski, the CB23 and D23 cell lines, were negative for ErbB1, in other words, EGFR. *See Pinkas-Kramarski* at 1250, col.2 – 1251, col. 1. However, the claims at issue require that the cells express EGFR. Therefore, it is difficult to understand how this disclosure can be used in the present rejection.

More importantly, the Office Action highlighted the fact that EGF and betacellulin, two EGFR ligands, were able to bind the HER-2/HER-3 heterodimer. However, the Office Action failed to acknowledge that all of the other EGFR ligands tested, such as TGFα, HB-EGF, or AR were not able to induce a proliferative signal through this heterodimer. In other words, less than half of the EGFR ligands were able to induce a proliferative signal. Moreover, of the two EGFR ligands that were capable of eliciting a proliferative response in the absence of EGFR, both could only do so at high concentrations of ligand. *See Pinkas-Kramarski* at 1251. Further, Pinkas-Kramarski failed to indicate whether the 5×10^{-8} M or higher concentration of ligand required to detect activity of the heterodimer was at all relevant to physiological levels of the ligand in tumors. And, more importantly, Pinkas-Kramarski found that neither of these two ligands could elicit such a response in cells "singly expressing ErbB-2 or ErbB-3, even when very high concentrations were used." *Pinkas-Kramarski* at 1252. In other words, both HER-2 and HER-3 are required to elicit a proliferative response. However, the present claims only require that the

expression levels of HER-3 be detected in the assay because one (non-limiting) aspect of the present invention is that HER-3 levels are sufficient to provide for anti-EGFR antibody treatment in cancers comprising cells that express EGFR. Instead, one skilled in the art would understand Pinkas-Kramarski as teaching that both HER-3 and HER-2 levels must be monitored in order to determine if the two ligands could elicit a proliferative response. One of skill in the art would simply have had no assurance from the teaching of Pinkas-Kramarski that if EGFR were inhibited, any particular EGFR ligand would be able to stimulate growth of cancer cells via HER-3.

The deficiencies of Hudziak, Esteva and Pinkas-Kramarski are not overcome by the combination with Hoffmann. At the outset, Applicants note that the Office Action only cited to the abstract of Hoffman, even though according to the internal guidelines of the Patent Office, "[c]itation of and reliance upon an abstract without citation of and reliance upon the underlying scientific document is generally inappropriate where both the abstract and the underlying document are prior art." M.P.E.P. 706.02(II). The M.P.E.P. indicates that it is only appropriate under limited circumstances to make a rejection in a non-final Office Action based in whole or in part on the abstract only without relying on the full text document. *Id.* This is because it is possible "that the full text document will include teachings away from the invention that will preclude an obviousness rejection under 35 U.S.C. 103, when the abstract alone appears to support the rejection." Therefore, Applicants submit the underlying full text document of Hoffmann with this Response and respectfully request it be given thorough consideration and that it be cited of record in the prosecution history of the present application.

Hoffman is cited as teaching that expression of receptors such as ErbB-2 and ErbB-3 are associated with TNF-alpha insensitivity. However, Applicants again note that immortalized cell

lines were used in Hoffman, and as described above, immortalized cell lines do not necessary correlate with the activity of primary cells from a subject as required by the present claims. In addition, Hoffman noted that TNF-α resistance was based on either the expression of EGFR or the expression of both ErbB2 and ErbB3 (HER-2 and HER-3). As noted above, the present claims only require that the expression levels of HER-3 be detected in the assay because one (non-limiting) aspect of the present invention is that HER-3 levels are sufficient to identify subjects with cancer that can be treated with an anti-EGFR antibody. However, one skilled in the art would understand Hoffman as teaching that both HER-3 and HER-2 levels must be monitored in order to determine if the two ligands could elicit a proliferative response. Finally, Hoffman teaches treatment with TNF-α, not an antibody therapy, much less a therapy based on and anti-EGFR antibody. Therefore, one of skill in the art would not understand Hoffman as teaching that HER-3 alone could be monitored for susceptibility to TNF-α treatment, much less the anti-EGFR antibody therapy as required by the present claims.

The Office Action did not specifically respond to Applicants' position that if, in fact, Esteva teaches that HER3 is activated by ligands that are specific for the HER receptor, a position the Office Action has taken, than one of skill in the art would have concluded that *high levels* of HER3 expression would have identified subjects to treat with anti-EGFR antibodies. This is because a skilled artisan would have understood that if HER3 is know be activated by ligands for EGFR, then HER-3 likely or possibly also reacts with anti-EGFR antibodies. However, the present application was the first to teach that it was actually lower levels of expression of HER3 that can be used to identify these subjects. Therefore, if Esteva does, in fact, teach that HER3 is activated by ligands for other HER receptors, as alleged by the Office Action, than it necessarily teaches away from the claimed invention.

The Office Action takes the position that the prior art demonstrates that EGFR ligands stimulate growth of cancer cells via HER-3, and that it is reasonable to expect that inhibition of only EGFR might be a less effective therapy than if the anti-EGFR therapy was provided to a tumor with only EGFR signaling to provide a growth signal to the tumor. However, again, the present invention is not claiming the use of an anti-EGFR antibody when EGFR is the only signal, but instead is claiming the detection of the expression level of HER3 to determine whether to treat a subject with an anti-EGFR antibody. As already explained above, none of the references, either alone or in combination, would teach or suggest to one of skill in the art that the susceptibility of a cancer comprising cells that express EGFR to an anti-EGFR antibody could be determined solely based on detecting the expression level for HER3. Therefore, the Office Action still has not provided a reason why the present invention would have been predictable to a skilled artisan in view of the cited art.

Thus, the Office Action has failed to establish a *prima facie* case of obviousness because first, a skilled artisan would not have been motivated to combine these two references, and second, even if the references were improperly combined, all of claim limitations are not even taught or suggested by the combination of Hudziak, Esteva Pinkas-Kramarski and Hoffmann. Therefore, Applicants respectfully request reconsideration and withdrawal of the rejection.

Claims 29-34 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Hudziak in view of Esteva, Pinkas-Kramarski or Hoffmann, and further in view of Yang, W.-D *et al.*, Critical Reviews on Oncology/Hematology, 38: 17-23 (2001) ("Yang"). The Applicants traverse the rejection.

As explained above, the combination of references cited by the Patent Office does not teach, suggest, or make obvious all of the claims limitations of claim 29. The combination of references does not teach, disclose or make obvious at least the following limitation of claim 29: "treating the subject with an anti-EGFR antibody if HER3 expression levels are detected having an optical density less than 9 when determined by quantitative immunohistochemistry."

The additionally cited reference, taken alone or in any combination with the earlier-discussed references, do not teach or suggest the instantly claimed method. The teachings and deficiencies, as related to the present invention, of Hudziak, Esteva, Pinkas-Kramarski, and Hoffmann are thoroughly discussed above. The deficiencies of Hudziak, Esteva, Pinkas-Kramarski and Hoffmann are not overcome by the combination with Yang. In this ground of rejection, Yang is cited additionally as teaching the ABX-0303 antibody. However, Yang does not teach or suggest that HER3 can be used as a biomarker for the use of the ABX-0303, much less treating a subject with ABX-0303 if HER3 expression levels are detected having an optical density less than 9 when determined by quantitative immunohistochemistry.

As a result, Yang's combination with Hudziak, Esteva, Pinkas-Kramarski and Hoffmann can not teach or suggest all of the claim limitations. Thus, the Patent Office has not established a *prima facie* case of obviousness of claim 29 based on the cited references. As rejected claims 30-34 depend from claim 29, thereby sharing the above limitations, the cited references also cannot render these claims obvious. Therefore, Applicants respectfully request reconsideration and withdrawal of the rejection.

CONCLUSION

Based on all of the above, the Applicants believe the claims are now allowable. If there are any questions or comments regarding this response, the Patent office is encouraged to contact the undersigned agent as indicated below.

Respectfully submitted,

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